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| (21) International Application Number: PCT/EP99/04546 (22) International Filing Date: 30 June 1999 (30.06.99) (30) Priority Data: 98202258.4 6 July 1998 (06.07.98) EP (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): END, David, William [US/US]; Janssen Research Foundation, Welsh and McKean Roads, Spring House, PA 19477-0776 (US). COOLS, Marina, Lucie, Louise [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VAN WAUWE, Jean, Pierre, Frans [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). (74) Agent: QUAGHEBEUR, Luc; Patent Dept. - ext. 3547, Turnhoutseweg 30, B-2340 Beerse (BE). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITORS FOR TREATING ARTHROPATHIES (57) Abstract The present invention is concerned with the finding that farnesyl protein transferase inhibitors are useful for preparing a pharmaceutical composition for treating arthropathies such as rheumatoid arthritis, osteoarthritis, juvenile arthritis, and gout. | | |

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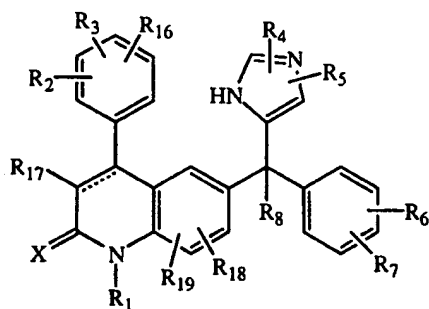
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Farnesyl protein transferase inhibitors for treating arthropathies

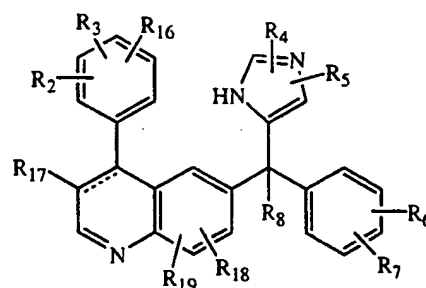
The present invention is concerned with the finding that farnesyl protein transferase inhibitors are useful for preparing a pharmaceutical composition for treating arthropathies such as, for example, rheumatoid arthritis, osteoarthritis, juvenile arthritis, and gout.

In Arthritis and Rheumatism, 40 (9), 1997, 1636-1643, Roivanen *et al.* describe H-*ras* oncogene point mutations in arthritic (and in healthy) synovium. Mutations in codon 13 and unexpectedly also in codon 14 could be detected in arthritic synovia from patients with rheumatoid arthritis, osteoarthritis and other arthropathies, but also in the synovia of controls without any joint disease. Whether the mutations have any importance in the pathogenesis of joint diseases therefore remains unanswered.

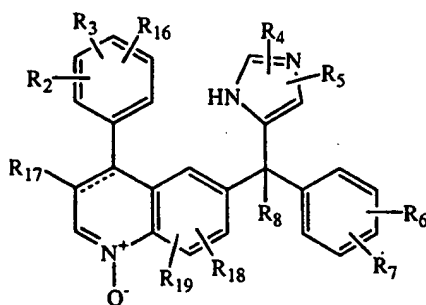
WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized *in vivo* to the compounds of formula (I). The compounds of formulas (I), (II) and (III) are represented by



(I)



(II)



(III)

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the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

- 5 R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, amino C_{1-6} alkyl,

or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,

wherein Alk^1 is C_{1-6} alkanediyl,

- 10 R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2 oxy,

- 15 Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, 4,4-dimethyloxazolyl; or

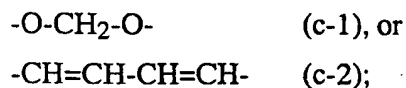
when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

- 20 $-O-CH_2-O-$ (a-1),
 $-O-CH_2-CH_2-O-$ (a-2),
 $-O-CH=CH-$ (a-3),
 $-O-CH_2-CH_2-$ (a-4),
 $-O-CH_2-CH_2-CH_2-$ (a-5), or
 $-CH=CH-CH=CH-$ (a-6);

- 25 R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, Ar^2 oxy, trihalomethyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, or

- 30 when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula



R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl,

- 35 C_{1-6} alkylcarbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, carboxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-

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aminoC₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, or a radical of formula

-O-R¹⁰ (b-1),

-S-R¹⁰ (b-2),

5 -N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

10 R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, 15 amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

wherein Alk² is C₁₋₆alkanediyl;

R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxy-C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

20 R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;

R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

25 R¹⁹ is hydrogen or C₁₋₆alkyl;

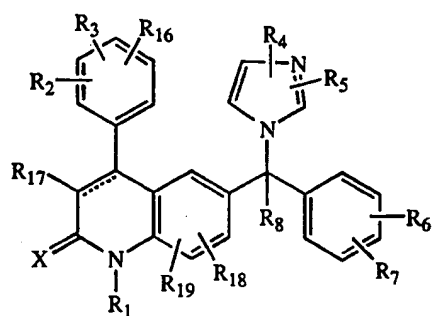
Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

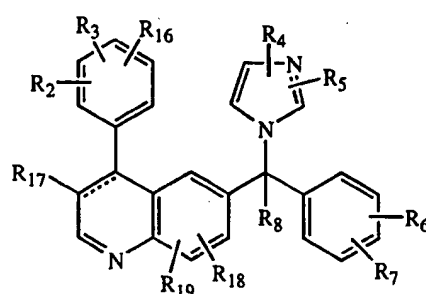
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WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized *in vivo* to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by

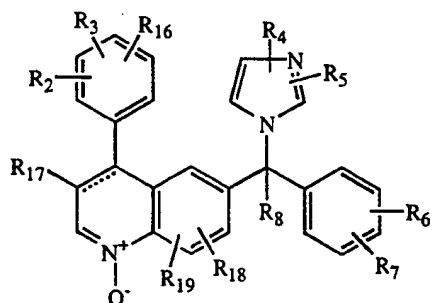
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(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein the dotted line represents an optional bond;

X is oxygen or sulfur;

R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinyC₁₋₆alkyl, pyridylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

R² and R³ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, amino-C₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy, Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl; or

when on adjacent positions R² and R³ taken together may form a bivalent radical of formula

-O-CH₂-O- (a-1),

-O-CH₂-CH₂-O- (a-2),

-O-CH=CH- (a-3),

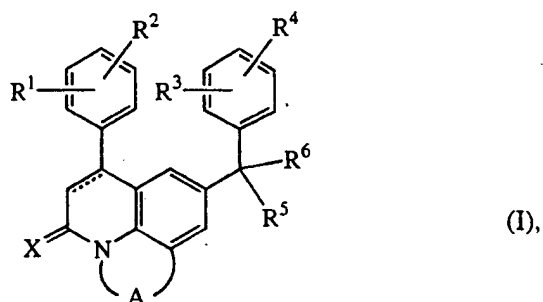
-5-

- O-CH₂-CH₂- (a-4),
 -O-CH₂-CH₂-CH₂- (a-5), or
 -CH=CH-CH=CH- (a-6);

- R⁴ and R⁵ each independently are hydrogen, Ar¹, C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl,
 5 C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl,
 C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;
 R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy or
 Ar²oxy;
 R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl-
 10 carbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, hydroxy-
 carbonylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-
 aminoC₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl,
 Ar¹, Ar²C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl;
 R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;
 15 R¹¹ is hydrogen or C₁₋₆alkyl;
 Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or
 halo;
 Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or
 halo.

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PCT/EP98/01296, filed 3 March 1998, concerns the preparation, formulation and
 pharmaceutical properties of farnesyl protein transferase inhibiting compounds of
 formula (VII)



- 25 the pharmaceutically acceptable acid addition salts and the stereochemically isomeric
 forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

- 30 -A- is a bivalent radical of formula

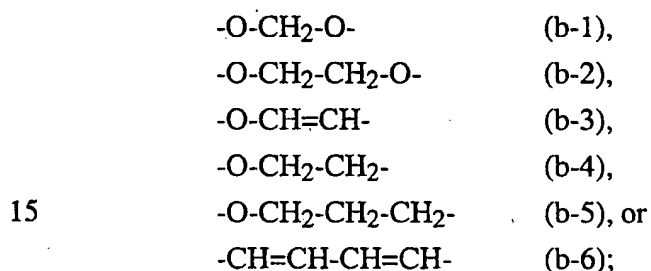
- | | | | |
|-------------------------------------|--------|---------------------------------------|--------|
| -CH=CH- | (a-1), | -CH ₂ -S- | (a-6), |
| -CH ₂ -CH ₂ - | (a-2), | -CH ₂ -CH ₂ -S- | (a-7), |

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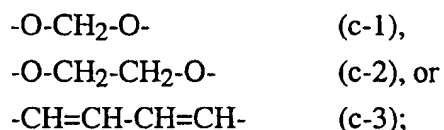


wherein optionally one hydrogen atom may be replaced by C₁₋₄alkyl or Ar¹;

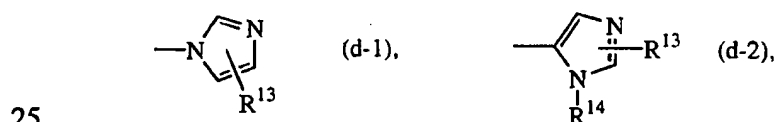
- 5 R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar², Ar²-C₁₋₆alkyl, Ar²-oxy, Ar²-C₁₋₆alkyloxy; or when on adjacent positions R¹ and R² taken together may form a bivalent radical of formula



- 15 R³ and R⁴ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar³-oxy, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R³ and R⁴ taken together may form a bivalent radical of formula



20 R⁵ is a radical of formula



25 wherein R¹³ is hydrogen, halo, Ar⁴, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxy-C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl or di(C₁₋₄alkyl)aminosulfonyl;

- 30 R⁶ is hydrogen, hydroxy, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, Ar⁵, Ar⁵-C₁₋₆alkyloxyC₁₋₆alkyl; or a radical of formula

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-O-R⁷ (e-1),-S-R⁷ (e-2),-N-R⁸R⁹ (e-3),

wherein R⁷ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar⁶, Ar⁶-C₁-6alkyl,
 5 C₁-6alkyloxycarbonylC₁-6alkyl, or a radical of formula -Alk-OR¹⁰ or
 -Alk-NR¹¹R¹²;

R⁸ is hydrogen, C₁-6alkyl, Ar⁷ or Ar⁷-C₁-6alkyl;

R⁹ is hydrogen; C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl,
 C₁-6alkylaminocarbonyl, Ar⁸, Ar⁸-C₁-6alkyl, C₁-6alkylcarbonyl-
 10 C₁-6alkyl, Ar⁸-carbonyl, Ar⁸-C₁-6alkylcarbonyl, aminocarbonyl-
 carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy,
 aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino,
 C₁-6alkylamino, C₁-6alkylcarbonylamino,
 or a radical or formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

wherein Alk is C₁-6alkanediyl;

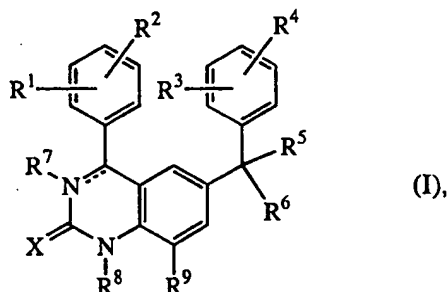
R¹⁰ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-
 C₁-6alkyl, Ar⁹ or Ar⁹-C₁-6alkyl;

R¹¹ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹⁰ or
 Ar¹⁰-C₁-6alkyl;

R¹² is hydrogen, C₁-6alkyl, Ar¹¹ or Ar¹¹-C₁-6alkyl; and

Ar¹ to Ar¹¹ are each independently selected from phenyl; or phenyl substituted with
 halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl.

PCT/EP98/02357, filed 17 April 1998, concerns the preparation, formulation and
 25 pharmaceutical properties of farnesyl protein transferase inhibiting compounds of
 formula (VIII)



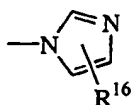
the pharmaceutically acceptable acid addition salts and the stereochemically isomeric
 forms thereof, wherein

30 the dotted line represents an optional bond;

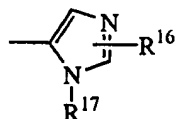
X is oxygen or sulfur;

- R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar¹C₁₋₆alkyl, Ar¹oxy or Ar¹C₁₋₆alkyloxy;
- 5 R³ and R⁴ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar¹oxy, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, trihalomethyl or trihalomethoxy;
- R⁵ is hydrogen, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonyl-
- 10 C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, Ar¹, Ar¹C₁₋₆alkyloxyC₁₋₆alkyl; or a radical of formula
- O-R¹⁰ (a-1),
- S-R¹⁰ (a-2),
- N-R¹¹R¹² (a-3),
- 15 wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar¹C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;
- R¹¹ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar¹C₁₋₆alkyl;
- R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl,
- 20 C₁₋₆alkylaminocarbonyl, Ar¹, Ar¹C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, Ar¹carbonyl, Ar¹C₁₋₆alkylcarbonyl, aminocarbonyl-carbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino,
- 25 or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;
- wherein Alk is C₁₋₆alkanediyl;
- R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxy-C₁₋₆alkyl, Ar¹ or Ar¹C₁₋₆alkyl;
- R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar¹C₁₋₆alkyl;
- 30 R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar¹C₁₋₆alkyl;

R⁶ is a radical of formula



(b-1),



(b-2),

wherein R¹⁶ is hydrogen, halo, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxy-

35 C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, C₁₋₆alkyloxycarbonyl,

C₁₋₆alkylthioC₁₋₆alkyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkyl-S(O)₂C₁₋₆alkyl;

R¹⁷ is hydrogen, C₁₋₆alkyl or di(C₁₋₄alkyl)aminosulfonyl;

R⁷ is hydrogen or C₁₋₆alkyl provided that the dotted line does not represent a bond;

5 R⁸ is hydrogen, C₁₋₆alkyl or Ar²CH₂ or Het¹CH₂;

R⁹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo; or

R⁸ and R⁹ taken together to form a bivalent radical of formula

-CH=CH- (c-1),

-CH₂-CH₂- (c-2),

10 -CH₂-CH₂-CH₂- (c-3),

-CH₂-O- (c-4), or

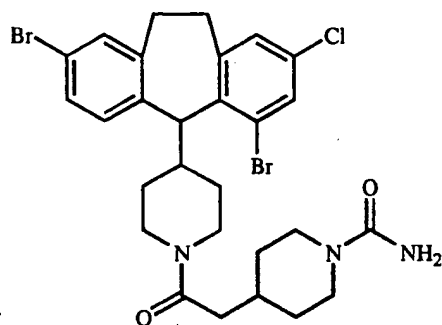
-CH₂-CH₂-O- (c-5);

Ar¹ is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl;

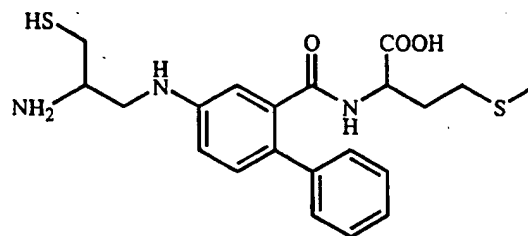
15 Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl; and

Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

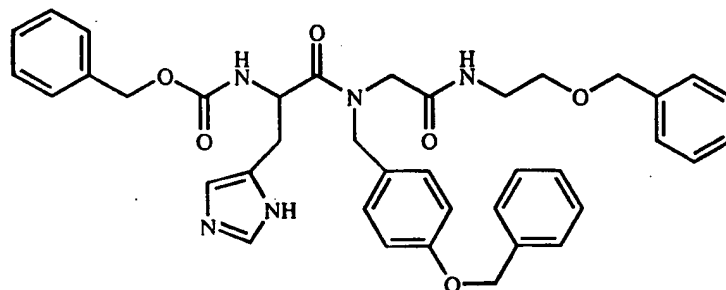
20 Other useful farnesyl protein transferase inhibitors have the structure :



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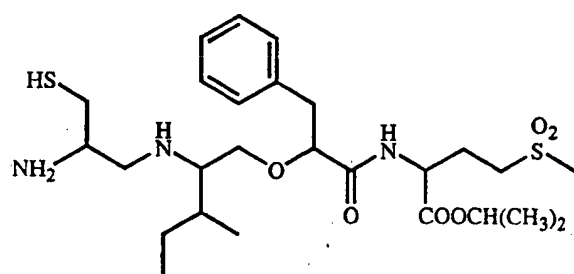


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These farnesyl protein transferase inhibitors decrease the growth of tumors *in vivo* by a direct effect on tumor cell growth but also indirectly, *i.e.* by inhibiting angiogenesis
 5 (Rak. J. *et al.*, Cancer Research, 55, 4575-4580, 1995). Consequently, treatment with these inhibitors suppresses solid tumor growth *in vivo* at least in part by inhibiting angiogenesis.

Unexpectedly, we have now found that farnesyl protein transferase inhibitors show *in*
 10 *vivo* activity against arthritis ; the beneficial effect can be attributed both to a decrease in the severity of the disease, as well as in the incidence.

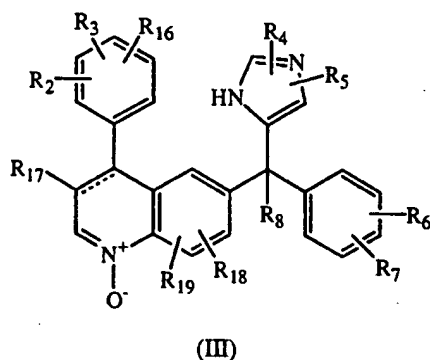
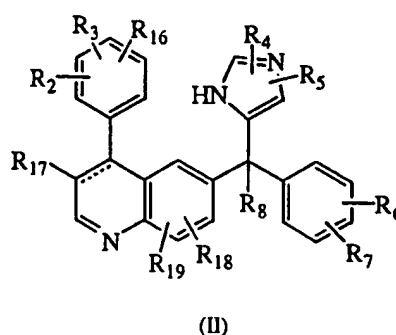
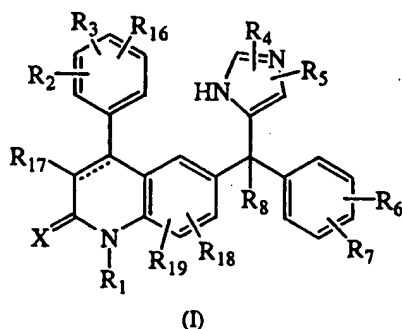
Arthritis, in particular rheumatoid arthritis, is one of several joint diseases collectively known as arthropathies. The diseases are characterized by hyperproliferation of the
 15 synovial membrane in the joint, the formation of pannus, and the destruction of cartilage and bone. Arthropathies comprise rheumatoid arthritis, osteoarthritis, juvenile arthritis, polyarthritis, gout, epidemic polyarthritis (Ross River Virus infection), psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus ; arthropathies can also be observed in Felty's syndrome, Reiter's syndrome and Still's syndrome.

20 Current therapy of arthropathies includes drugs such as steroids (*e.g.* prednisone), disease-modifying antirheumatic drugs (*e.g.* gold sodium thiomalate, methotrexate, hydroxychloroquine, sulfasalazine) and nonsteroidal antiinflammatory drugs; bed rest, splinting of the affected joints, application of local heat to the joint and physical
 25 therapy.

The present invention is concerned with the use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition for treating arthropathies.

30 In particular, the present invention is concerned with the use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition for treating arthropathies, wherein said farnesyl protein transferase inhibitor is an (imidazolyl-5-yl)methyl-2-quinolinone derivative of formula (I), or a compound of

formula (II) or (III) which is metabolized *in vivo* to the compound of formula (I), said compounds being represented by



5

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

- 10 R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridylC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, aminoC₁₋₆alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

- 15 R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy, Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazolyl; or

20

when on adjacent positions R² and R³ taken together may form a bivalent radical of formula

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- O-CH₂-O- (a-1),
 -O-CH₂-CH₂-O- (a-2),
 -O-CH=CH- (a-3),
 -O-CH₂-CH₂- (a-4),
 5 -O-CH₂-CH₂-CH₂- (a-5), or
 -CH=CH-CH=CH- (a-6);

- R⁴ and R⁵ each independently are hydrogen, halo, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl,
 C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl,
 C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;
 10 R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy,
 Ar²oxy, trihalomethyl, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, or
 when on adjacent positions R⁶ and R⁷ taken together may form a bivalent radical
 of formula

- O-CH₂-O- (c-1), or
 15 -CH=CH-CH=CH- (c-2);

- R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl-
 carbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, carboxy-
 C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino-
 C₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonyl-
 20 C₁₋₆alkyl, or a radical of formula

- O-R¹⁰ (b-1),
 -S-R¹⁰ (b-2),
 -N-R¹¹R¹² (b-3),

- wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl,
 25 C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³
 or -Alk²-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

- R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl,
 C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-
 30 C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl,
 aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy,
 C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl,
 amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino,
 or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;
 35 wherein Alk² is C₁₋₆alkanediyl;

R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxy-
 C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

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R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;

5 R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

R¹⁹ is hydrogen or C₁₋₆alkyl;

Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

10

In Formulas (I), (II) and (III), R⁴ or R⁵ may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R⁴ or R⁵ and the meaning of R⁴ and R⁵ when bound to the nitrogen is limited to hydrogen, Ar¹,
15 C₁₋₆alkyl, hydroxyc₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl, C₁₋₆alkylS(O)₂C₁₋₆alkyl.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C₁₋₆alkyl defines straight and branched chained saturated hydrocarbon
20 radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like; C₁₋₈alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C₁₋₆alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or octyl; C₁₋₁₂alkyl again encompasses C₁₋₈alkyl and the higher homologues thereof
25 containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C₁₋₁₆alkyl again encompasses C₁₋₁₂alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentadecyl and hexadecyl; C₂₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example,
30 ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a
35 carbonyl group, "S(O)" refers to a sulfoxide and "S(O)₂" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid

and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

5

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II) and (III) are able to form. The compounds of formulas (I), (II) and (III) which have basic properties can be
10 converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic,
15 fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The compounds of formulas (I), (II) and (III) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid
20 form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

25

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulas (I), (II) and (III) are able to form. Examples - of such forms are e.g. hydrates, alcoholates and the like.

30 The term stereochemically isomeric forms of compounds of formulas (I), (II) and (III), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulas (I), (II) and (III) may possess. Unless otherwise mentioned or indicated, the chemical designation
35 of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulas (I), (II) and (III) both in

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pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

5 Some of the compounds of formulas (I), (II) and (III) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

10 Whenever used hereinafter, the term "compounds of formulas (I), (II) and (III)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

Preferably the substituent R^{18} is situated on the 5 or 7 position of the quinolinone moiety and substituent R^{19} is situated on the 8 position when R^{18} is on the 7-position.

15 Interesting compounds are these compounds of formula (I) wherein X is oxygen.

Also interesting compounds are these compounds of formula (I) wherein the dotted line represents a bond, so as to form a double bond.

20 Another group of interesting compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, wherein Alk^1 is methylene and R^9 is C_{1-8} alkyl-amino substituted with C_{1-6} alkyloxycarbonyl.

25 Still another group of interesting compounds are those compounds of formula (I) wherein R^3 is hydrogen or halo; and R^2 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, trihalomethoxy or hydroxy C_{1-6} alkyloxy.

30 A further group of interesting compounds are those compounds of formula (I) wherein R^2 and R^3 are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R^5 is hydrogen and R^4 is hydrogen or C_{1-6} alkyl.

35

Yet another group of interesting compounds are those compounds of formula (I) wherein R^7 is hydrogen; and R^6 is C_{1-6} alkyl or halo, preferably chloro, especially 4-chloro.

A particular group of compounds are those compounds of formula (I) wherein R⁸ is hydrogen, hydroxy, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxy-carbonylC₁₋₆alkyl, imidazolyl, or a radical of formula -NR¹¹R¹² wherein R¹¹ is hydrogen or C₁₋₁₂alkyl and R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxy, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, or a radical of formula -Alk²-OR¹³ wherein R¹³ is hydrogen or C₁₋₆alkyl.

Preferred compounds are those compounds wherein R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, or a radical of formula -Alk¹-C(=O)-R⁹, wherein Alk¹ is methylene and R⁹ is C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl; R² is halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkyloxy, trihalo-methoxy, hydroxyC₁₋₆alkyloxy or Ar¹; R³ is hydrogen; R⁴ is methyl bound to the nitrogen in 3-position of the imidazole; R⁵ is hydrogen; R⁶ is chloro; R⁷ is hydrogen; R⁸ is hydrogen, hydroxy, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxy-carbonylC₁₋₆alkyl, imidazolyl, or a radical of formula -NR¹¹R¹² wherein R¹¹ is hydrogen or C₁₋₁₂alkyl and R¹² is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, or a radical of formula -Alk²-OR¹³ wherein R¹³ is C₁₋₆alkyl; R¹⁷ is hydrogen and R¹⁸ is hydrogen.

Most preferred compounds are
 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone,
 6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
 6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
 6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride monohydrate;
 6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone,
 6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and
 (+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound 75 in Table 1 of the Experimental part); or a pharmaceutically acceptable acid addition salt thereof.

Farnesyl protein transferase inhibitors can be formulated into pharmaceutical compositions as known in the art ; for the compounds of formulas (I), (II) and (III) suitable examples can be found in WO-97/21701. To prepare the aforementioned pharmaceutical compositions, a therapeutically effective amount of the particular
5 compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous, or parenteral
10 administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as
15 starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable
20 solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions containing compounds of formula (I) may be formulated in an oil for prolonged action. Appropriate oils for this purpose are, for example, peanut oil, sesame oil, cottonseed
25 oil, corn oil, soy bean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally
30 combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. As appropriate compositions for
35 topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by

aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

5 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity
10 of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

15 Preferably, a therapeutically effective amount of the pharmaceutical composition comprising a farnesyl protein transferase inhibitor is administered orally or parenterally. Said therapeutically effective amount is the amount that effectively decreases the severity of arthritis, *i.e.* diminishes the swelling and the tenderness of the joints and
20 reduces the pain, or the amount that reduces the incidence, *i.e.* the number of swollen and tender joints. On the basis of the current data, it appears that a pharmaceutical composition comprising (+)-6-[amino(4-chlorophenyl) (1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (compound 75) as the active ingredient can be administered orally in an amount of from 10 to 1500 mg daily,
25 either as a single dose or subdivided into more than one dose. A preferred amount ranges from 100 to 1,000 mg daily.

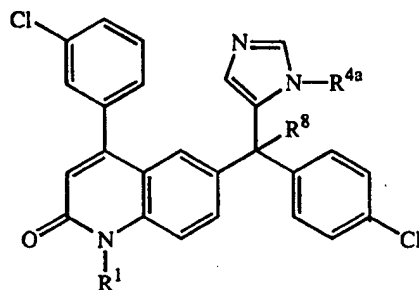
The therapy of arthropathies using farnesyl protein transferase inhibitors can conveniently be combined with drug therapies using steroids (*e.g.* prednisone), disease-modifying antirheumatic drugs (*e.g.* gold sodium thiomalate, methotrexate,
30 hydroxychloroquine, sulfasalazine) and nonsteroidal antiinflammatory drugs; bed rest, splinting of the affected joints, application of local heat to the joint and physical therapy.

35 The present invention also concerns a method of treating arthropathies in a mammal comprising the step of administering a therapeutically effective amount of a farnesyl protein transferase inhibitor to said mammal.

Experimental Part

The following tables show the formulas of the compounds of formula (I), their physical data, and references to the examples in WO-97/21701 according to which the compounds in question may be prepared. In the pharmacological example, the effect of

5 the compounds of formula (I) on induced arthritis is illustrated.

Table 1:

| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|-----------------|---|---|---|
| 3 | B.1 | CH ₃ | CH ₃ | OH | mp. 233.6°C |
| 4 | B.3 | CH ₃ | CH ₃ | OCH ₃ | mp. 140-160°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 5 | B.6 | CH ₃ | CH ₃ | H | mp. 165°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 6 | B.5 | CH ₃ | CH ₂ CH ₃ | H | mp. 180°C; .C ₂ H ₂ O ₄ .1/2H ₂ O |
| 7 | B.2 | H | CH ₃ | H | mp. 260°C |
| 8 | B.2 | H | (CH ₂) ₃ CH ₃ | OH | - |
| 9 | B.4 | CH ₃ | (CH ₂) ₃ CH ₃ | OH | mp. 174°C |
| 10 | B.3 | H | CH ₃ | OCH ₂ COOCH ₂ CH ₃ | mp. 185°C; .3/2C ₂ H ₂ O ₄ |
| 11 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ N(CH ₃) ₂ | mp. 120°C |
| 12 | B.7 | CH ₃ | CH ₃ | CH ₃ | mp. 210°C; .C ₂ H ₂ O ₄ |
| 13 | B.7 | CH ₃ | CH ₃ | CH ₂ CH ₃ | mp. 196°C; .C ₂ H ₂ O ₄ |
| 14 | B.13 | CH ₃ | CH ₃ | NH ₂ | mp. 220°C |
| 72 | B.13 | CH ₃ | CH ₃ | NH ₂ | .3/2-(E)-C ₄ H ₄ O ₄ |
| 73 | B.13 | CH ₃ | CH ₃ | NH ₂ | .2HCl |
| 74 | B.8b | CH ₃ | CH ₃ | NH ₂ | (A) |
| 75 | B.8b | CH ₃ | CH ₃ | NH ₂ | (+) |
| 15 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₃ OH | mp. 135°C |

| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|---|---|---|--|
| 16 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ CH ₃ | mp. 180°C; .C ₂ H ₂ O ₄ .3/2(H ₂ O) |
| 17 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ O-C ₆ H ₅ | mp. 144°C; .3/2(C ₂ H ₂ O ₄) |
| 18 | B.2 | H | CH(CH ₃) ₂ | OH | - |
| 19 | B.4 | CH ₃ | CH(CH ₃) ₂ | OH | mp. 254°C |
| 20 | B.2 | H | (CH ₂) ₂ OCH ₃ | OH | mp. 112°C |
| 21 | B.4 | CH ₃ | (CH ₂) ₂ OCH ₃ | OH | mp. 192°C |
| 22 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₂ OH | mp. 198°C |
| 23 | B.8a | CH ₃ | CH ₃ | OH | mp. 150-200°C; (A); .C ₂ H ₂ O ₄ |
| 24 | B.8a | CH ₃ | CH ₃ | OH | mp. 150-200°C; (B); .C ₂ H ₂ O ₄ |
| 25 | B.11 | CH ₃ | CH ₃ | CH ₂ -CN | mp. 154°C |
| 27 | B.2 | H | (CH ₂) ₃ OCH ₃ | OH | - |
| 28 | B.4 | CH ₃ | (CH ₂) ₃ OCH ₃ | OH | mp. 196°C; .H ₂ O |
| 29 | B.3 | CH ₃ | CH ₃ | O(CH ₂) ₃ OCH ₂ CH ₃ | mp. 105°C; .3/2(H ₂ O) |
| 31 | B.2 | H | CH ₃ | OH | > 260°C |
| 32 | B.6 | CH ₃ | (CH ₂) ₂ OCH ₃ | H | mp. 140°C; .3/2(C ₂ H ₂ O ₄) |
| 33 | B.6 | CH ₃ | (CH ₂) ₃ OCH ₃ | H | mp. 180°C; .HCl |
| 56 | B.12 | CH ₃ | CH ₃ | -NHCOCH ₃ | .C ₂ H ₂ O ₄ |
| 58 | B.11 | CH ₃ | CH ₃ | -CH ₂ COOCH ₂ CH ₃ | .C ₂ H ₂ O ₄ .3/2(H ₂ O) |
| 60 | B.11 | CH ₃ | CH ₃ | 1-imidazolyl | - |
| 61 | B.21 | CH ₃ | CH ₃ | -NH-CH ₃ | mp. 164°C |
| 65 | B.2 | H | (CH ₂) ₃ SOCH ₃ | OH | .H ₂ O |
| 66 | B.13 | CH ₃ | CH ₃ | -N(CH ₃) ₂ | .2C ₂ H ₂ O ₄ .H ₂ O mp. 160°C |
| 67 | B.13 | CH ₃ | CH ₃ | -NH-(CH ₂) ₂ OCH ₃ | mp. 216°C |
| 68 | B.13 | CH ₃ | CH ₃ | -NH-(CH ₂) ₂ -OH | - |
| 69 | B.7 | CH ₃ | CH ₃ | -CH ₂ Cl | .2C ₂ H ₂ O ₄ mp. 220°C |
| 70 | B.7 | CH ₃ | CH ₃ | -CH ₂ Br | - |
| 71 | * | CH ₃ | CH ₃ | -CH ₂ OH | .2C ₂ H ₂ O ₄ |
| 76 | B.4 | -(CH ₂) ₂ OCH ₃ | CH ₃ | OH | mp. 150°C |
| 77 | * | CH ₃ | CH ₃ | -CH ₂ OCH ₃ | .2C ₂ H ₂ O ₄ mp. 166°C |

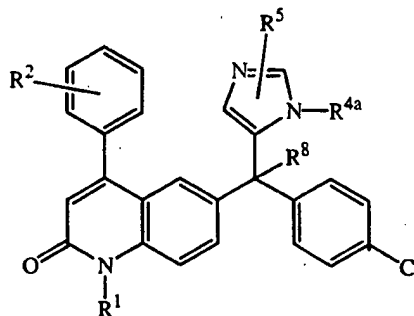
| Co. No. | Ex. No. | R ¹ | R ^{4a} | R ⁸ | Physical data |
|---------|---------|--|-----------------|---|--|
| 78 | B.13 | CH ₃ | CH ₃ | -NH-OCH ₃ | mp. 170°C |
| 79 | B.20 | CH ₃ | CH ₃ | -NH-CONH ₂ | .2H ₂ O |
| 80 | ** | CH ₃ | CH ₃ | -CH ₂ CONH ₂ | - |
| 81 | B.13 | CH ₃ | CH ₃ | -NH-OH | - |
| 82 | B.13 | CH ₃ | CH ₃ | -NH(CH ₂) ₂ N(CH ₃) ₂ | - |
| 83 | B.4 | (CH ₂) ₂ N(CH ₃) ₂ | CH ₃ | OH | .3/2C ₂ H ₂ O ₄ .3/2H ₂ O mp. 200 °C |
| 84 | * | CH ₃ | CH ₃ | -CH ₂ N(CH ₃) ₂ | .C ₂ H ₂ O ₄ mp. 210°C |
| 85 | B.4 | CH ₃ | CH ₃ | -N(CH ₃) ₂ | - |
| 86 | B.4 | CH ₃ | CH ₃ | NHCOCH ₂ N(CH ₃) ₂ | - |
| 87 | B.4 | CH ₃ | CH ₃ | -NH(CH ₂) ₉ CH ₃ | - |
| 88 | B.4 | CH ₃ | CH ₃ | -NH(CH ₂) ₂ NH ₂ | - |
| 89 | B.20 | CH ₃ | CH ₃ | -NHCOCH ₂ OCH ₃ | .HCl mp. 220°C |
| 90 | B.6 | CH ₃ | CH ₃ | H | - |
| 91 | B.20 | CH ₃ | CH ₃ | -NHCOCH ₂ C ₆ H ₅ | .C ₂ H ₂ O ₄ .H ₂ O mp. 170°C |
| 92 | B.20 | CH ₃ | CH ₃ | -NHCOC ₆ H ₅ | mp. 242°C |
| 93 | B.20 | CH ₃ | CH ₃ | -NHCOCONH ₂ | .C ₂ H ₂ O ₄ .H ₂ O mp. 186°C |
| 94 | B.13 | CH ₃ | CH ₃ | -NHC ₆ H ₅ | mp. 165°C |

* : prepared by functional-group transformation of compound 70

** : prepared by functional-group transformation of compound 25

Table 2:

5



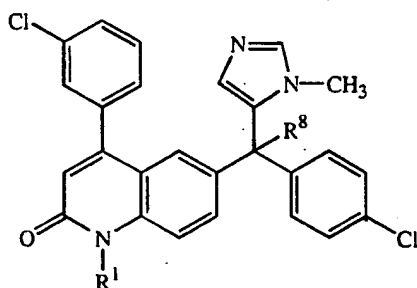
| Co. No. | Ex. No. | R ¹ | R ² | R ^{4a} | R ⁵ | R ⁸ | Physical data |
|---------|---------|-----------------|---|-----------------|-------------------|-----------------|--|
| 1 | B.1 | CH ₃ | H | CH ₃ | H | OH | mp. >250°C |
| 2 | B.5 | CH ₃ | H | CH ₃ | H | H | mp. 100-110°C |
| 26 | B.1 | CH ₃ | 3-Cl | CH ₃ | 2-CH ₃ | OH | mp. 200°C |
| 30 | B.6 | CH ₃ | 3-Cl | CH ₃ | 2-CH ₃ | H | mp. 120-140°C; .3/2(C ₂ H ₂ O ₄).H ₂ O |
| 34 | B.1 | CH ₃ | 3-O-CH ₂ -CH ₃ | CH ₃ | H | OH | mp. 190°C |
| 35 | B.6 | CH ₃ | 3-O-CH ₂ -CH ₃ | CH ₃ | H | H | mp. 160-180°C; .HCl.H ₂ O |
| 36 | B.1 | CH ₃ | 3-O-CH ₃ | CH ₃ | H | OH | mp. 210°C |
| 37 | B.1 | CH ₃ | 3-O-(CH ₂) ₂ -CH ₃ | CH ₃ | H | OH | mp. 150-160°C |
| 38 | B.1 | CH ₃ | 3-O-(CH ₂) ₃ -CH ₃ | CH ₃ | H | OH | mp. 150-160°C |
| 49 | B.1 | CH ₃ | 4-O-CH ₂ -CH ₃ | CH ₃ | H | OH | mp. 184.2°C |
| 50 | B.1 | CH ₃ | 3-O-CH-(CH ₃) ₂ | CH ₃ | H | OH | mp. 147.1°C |
| 51 | B.6 | CH ₃ | 3-O-(CH ₂) ₃ -CH ₃ | CH ₃ | H | H | mp. 164.2°C; .3/2(C ₂ H ₂ O ₄) |
| 52 | B.6 | CH ₃ | 3-O-(CH ₂) ₂ -CH ₃ | CH ₃ | H | H | .3/2(C ₂ H ₂ O ₄) |
| 53 | B.6 | CH ₃ | 3-O-CH-(CH ₃) ₂ | CH ₃ | H | H | mp. 133.9°C; .C ₂ H ₂ O ₄ .H ₂ O |
| 54 | B.14 | CH ₃ | 3-OH | CH ₃ | H | OH | - |
| 64 | B.10 | CH ₃ | 3-OH | CH ₃ | H | OH | .HCl.H ₂ O |
| 55 | B.6 | CH ₃ | 3-OH | CH ₃ | H | H | mp. >250°C |
| 57 | B.1 | CH ₃ | 2-OCH ₂ CH ₃ | CH ₃ | H | OH | - |
| 59 | B.13 | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | - |
| 95 | B.8a | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | (A) |
| 96 | B.8a | CH ₃ | 3-OCH ₂ CH ₃ | CH ₃ | H | NH ₂ | (B) |
| 62 | B.15 | CH ₃ | 3-O(CH ₂) ₂ N(CH ₃) ₂ | CH ₃ | H | OH | - |
| 63 | B.11 | CH ₃ | 3-O(CH ₂) ₂ -OH | CH ₃ | H | OH | - |
| 97 | B.1 | CH ₃ | 3-CH ₂ CH ₃ | CH ₃ | H | OH | - |
| 98 | B.13 | CH ₃ | 3-CH ₂ CH ₃ | CH ₃ | H | NH ₂ | mp. 240°C |
| 99 | B.1 | CH ₃ | 3-(CH ₂) ₂ CH ₃ | CH ₃ | H | OH | - |
| 100 | B.13 | CH ₃ | 3-(CH ₂) ₂ CH ₃ | CH ₃ | H | NH ₂ | - |
| 101 | * | CH ₃ | 3-O-(CH ₂) ₂ OCH ₃ | CH ₃ | H | OH | .3/2(C ₂ H ₂ O ₄) mp. 193°C |
| 102 | B.1 | CH ₃ | 3-CH ₃ | CH ₃ | H | OH | mp. >250°C |
| 103 | B.13 | CH ₃ | 3-CH ₃ | CH ₃ | H | NH ₂ | - |
| 104 | B.1 | CH ₃ | 3-Br | CH ₃ | H | OH | - |
| 105 | B.13 | CH ₃ | 3-Br | CH ₃ | H | NH ₂ | - |

| Co. No. | Ex. No. | R ¹ | R ² | R ^{4a} | R ⁵ | R ⁸ | Physical data |
|---------|---------|-----------------|---------------------------------|-----------------|-------------------|-----------------|---------------|
| 106 | B.1 | CH ₃ | 3-O-CF ₃ | CH ₃ | H | OH | - |
| 107 | B.13 | CH ₃ | 3-O-CF ₃ | CH ₃ | H | NH ₂ | mp. 168°C |
| 108 | B.1 | CH ₃ | 3-C ₆ H ₅ | CH ₃ | H | OH | - |
| 109 | B.13 | CH ₃ | 3-C ₆ H ₅ | CH ₃ | H | NH ₂ | - |
| 110 | B.1 | CH ₃ | 3-F | CH ₃ | H | OH | - |
| 111 | B.13 | CH ₃ | 3-F | CH ₃ | H | NH ₂ | mp. >250°C |
| 112 | B.1 | CH ₃ | 3-(E)-CH=CH-CH ₃ | CH ₃ | H | OH | mp. >250°C |
| 113 | B.2 | H | 3-Cl | CH ₃ | 3-Cl | OH | - |
| 114 | B.4 | CH ₃ | 3-Cl | CH ₃ | 3-Cl | OH | - |
| 115 | B.1 | CH ₃ | 3-Cl | H | 3-CH ₃ | OH | - |
| 116 | B.4 | CH ₃ | 3-Cl | CH ₃ | 3-CH ₃ | OH | - |
| 117 | ** | CH ₃ | 3-CN | CH ₃ | H | OH | - |
| 160 | B.1 | CH ₃ | 3-CF ₃ | CH ₃ | H | OH | - |

* : prepared by functional-group transformation of compound 54

** : prepared by functional-group transformation of compound 104

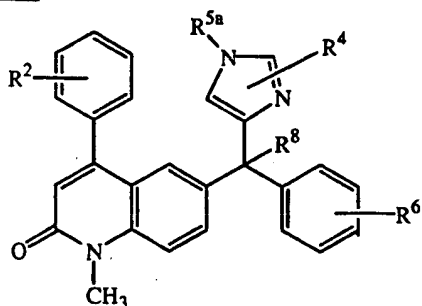
Table 3 :



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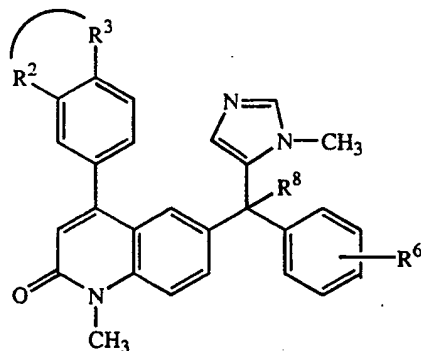
| Co. No. | Ex. No. | R ¹ | R ⁸ | Physical data |
|---------|---------|---|----------------|-------------------|
| 39 | B.4 | CH ₂ CONHCH(COOCH ₃)(CH ₂ CH(CH ₃) ₂) | H | mp. 240°C (S) |
| 40 | B.4 | CH ₂ -2-quinoliny | H | mp. 240°C; .2 HCl |
| 41 | B.4 | CH ₂ CONHCH(COOCH ₃)(CH ₂ CH(CH ₃) ₂) | OH | mp. > 260°C (S) |

Table 4 :



| Co. No. | Ex. No. | R ² | R ⁴ | R ^{5a} | R ⁶ | R ⁸ | Physical data |
|---------|---------|----------------|-------------------|---------------------------------|----------------|----------------|---|
| 42 | B.6 | H | H | H | 4-Cl | H | mp. 170°C; .C ₂ H ₂ O ₄ .1/2 H ₂ O |
| 43 | B.10 | H | H | H | 4-Cl | OH | mp. 180°C; .H ₂ O |
| 44 | B.5 | H | H | CH ₃ | 4-Cl | H | mp. 152°C |
| 45 | B.6 | 3-Cl | H | H | 4-Cl | H | mp. 175°C; .C ₂ H ₂ O ₄ |
| 46 | B.5 | 3-Cl | H | CH ₂ CH ₃ | 4-Cl | H | mp. 132°C; .C ₂ H ₂ O ₄ |
| 47 | B.5 | 3-Cl | H | CH ₃ | 4-Cl | H | mp. 115°C; .3/2 C ₂ H ₂ O ₄ |
| 48 | B.9 | 3-Cl | H | CH ₃ | 4-Cl | OH | mp. 230°C |
| 118 | B.4 | 3-Cl | 3-CH ₃ | CH ₃ | 4-Cl | OH | mp. 222°C |

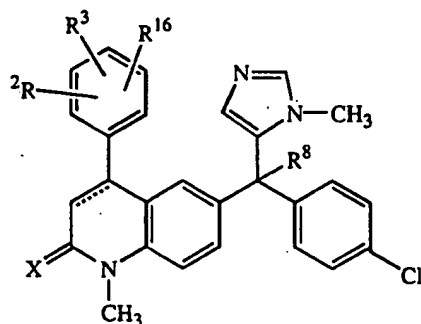
Table 5 :



5

| Co. No. | Ex. No. | -R ² -R ³ - | R ⁶ | R ⁸ |
|---------|---------|---|----------------|-----------------|
| 119 | B.1 | -O-CH ₂ -O- | 4-Cl | OH |
| 120 | B.13 | -O-CH ₂ -O- | 4-Cl | NH ₂ |
| 121 | B.1 | -O-CH ₂ -CH ₂ -O- | 4-Cl | OH |
| 122 | B.13 | -O-CH ₂ -CH ₂ -O- | 4-Cl | NH ₂ |
| 123 | B.1 | -O-CH=CH- | 4-Cl | OH |

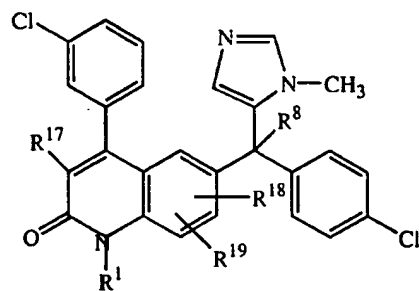
Table 6:



| Co. No. | Ex. No. | X | ----- | R ² | R ³ | R ¹⁶ | R ⁸ | Physical data |
|---------|---------|---|--------|--------------------|--------------------|--------------------|-----------------|--|
| 124 | B.1 | O | double | 3-OCH ₃ | 4-OCH ₃ | 5-OCH ₃ | OH | mp. 230°C |
| 125 | B.13 | O | double | 3-OCH ₃ | 4-OCH ₃ | 5-OCH ₃ | NH ₂ | mp. 218°C |
| 126 | B.1 | O | single | 3-Cl | H | H | OH | .C ₂ H ₂ O ₄ mp. 160°C |
| 127 | B.1 | O | single | 3-Cl | H | H | OH | - |
| 128 | B.16 | S | double | 3-Cl | H | H | H | - |

5

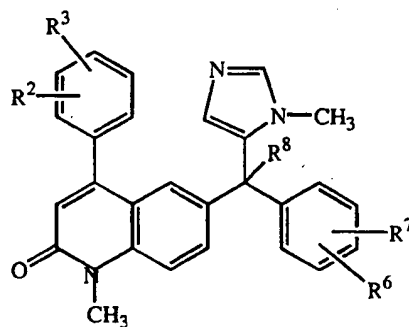
Table 7:



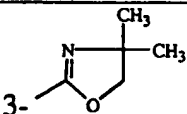
| Co. No. | Ex. No. | R ¹ | R ¹⁷ | R ¹⁸ | R ¹⁹ | R ⁸ | Physical data |
|---------|---------|-----------------|-----------------|-----------------|-----------------|---------------------|---------------|
| 129 | B.17 | H | CN | H | H | H | - |
| 130 | B.4 | CH ₃ | CN | H | H | H | mp. 202°C |
| 131 | B.17 | H | CN | H | H | OH | - |
| 132 | B.4 | CH ₃ | CN | H | H | OH | - |
| 133 | B.17 | H | CN | H | H | -CH ₂ CN | - |
| 134 | B.4 | CH ₃ | CN | H | H | -CH ₂ CN | mp. 138°C |
| 135 | B.18 | H | CH ₃ | H | H | OH | - |
| 136 | B.4 | CH ₃ | CH ₃ | H | H | OH | - |
| 137 | B.13 | CH ₃ | CH ₃ | H | H | NH ₂ | mp. >250°C |

| Co. No. | Ex. No. | R ¹ | R ¹⁷ | R ¹⁸ | R ¹⁹ | R ⁸ | Physical data |
|---------|---------|-----------------|-------------------------------------|--------------------|-------------------|-----------------|--|
| 138 | B.18 | H | C ₆ H ₅ | H | H | H | - |
| 139 | B.4 | CH ₃ | C ₆ H ₅ | H | H | H | .3/2(C ₂ H ₂ O ₄) mp. 180°C |
| 140 | B.18 | H | C ₆ H ₅ | H | H | OH | - |
| 141 | B.4 | CH ₃ | C ₆ H ₅ | H | H | OH | - |
| 142 | B.13 | CH ₃ | C ₆ H ₅ | H | H | NH ₂ | - |
| 143 | B.13 | CH ₃ | Cl | H | H | NH ₂ | - |
| 144 | B.17 | H | -COOCH ₂ CH ₃ | H | H | OH | - |
| 145 | B.4 | CH ₃ | -COOCH ₂ CH ₃ | H | H | OH | - |
| 146 | B.1 | CH ₃ | H | 8-CH ₃ | H | OH | - |
| 147 | B.13 | CH ₃ | H | 8-CH ₃ | H | NH ₂ | .H ₂ O |
| 148 | B.1 | CH ₃ | H | 7-Cl | H | OH | - |
| 149 | B.1 | CH ₃ | H | 7-CH ₃ | H | OH | - |
| 150 | B.1 | CH ₃ | H | 5-CH ₃ | H | OH | - |
| 151 | B.1 | CH ₃ | H | 8-OCH ₃ | H | OH | - |
| 161 | B.1 | CH ₃ | H | 7-CH ₃ | 8-CH ₃ | OH | mp. 255°C |

Table 8 :



| Co. No. | Ex. No. | R ² | R ³ | R ⁶ | R ⁷ | R ⁸ | Physical data |
|---------|---------|------------------------------------|----------------|------------------------------------|----------------|----------------|---|
| 152 | B.1 | 3-OCH ₂ CH ₃ | H | 4-OCH ₂ CH ₃ | H | OH | .3/2(C ₂ H ₂ O ₄) |
| 153 | B.1 | 3-Cl | H | H | H | OH | - |
| 154 | B.1 | 3-Cl | H | 4-CH ₃ | H | OH | - |
| 155 | B.1 | 3-Cl | H | 4-OCH ₃ | H | OH | - |
| 156 | B.1 | 3-Cl | H | 4-CF ₃ | H | OH | - |
| 157 | B.1 | 3-Cl | H | 2-Cl | 4-Cl | OH | - |
| 158 | B.1 | 3-Cl | 5-Cl | 4-Cl | H | OH | - |

| Co. No. | Ex. No. | R ² | R ³ | R ⁶ | R ⁷ | R ⁸ | Physical data |
|---------|---------|---|----------------|------------------------------------|----------------|----------------|--|
| 159 | B.1 |  | H | 4-Cl | H | OH | - |
| 162 | B.1 | 3-Cl | H | 4-S-CH ₃ | H | OH | mp. 169°C .C ₂ H ₂ O ₄ .H ₂ O; mp.decomposes > 172°C .C ₂ H ₂ O ₄ |
| 163 | B.1 | 3-Cl | H | 4-N(CH ₃) ₂ | H | OH | |
| 164 | B.1 | 3-Cl | H | -CH=CH-CH=CH- * | | OH | |

* : R⁶ and R⁷ taken together to form a bivalent radical between positions 3 and 4 on the phenyl moiety

Pharmacological examples

5 Example 1 : Prophylactic treatment

- Male DBA1/J mice were immunized intradermally with collagen type II emulsified in complete Freund's Adjuvant on day 0 and day 21. Treatment of mice was started on day 20 (10 animals/treatment group). Mice were treated orally twice daily (6 hours time interval) with vehicle [DMSO : cremophor : 0.9 % NaCl solution, 1:1:8 (v:v:v)] or compound 75 at a dose of 100 mg/kg. Three times per week symptoms of arthritis were scored. Animals were treated till day 36, at day 37 animals were sacrificed, blood was collected for analysis of anti-collagen antibodies, radiographs were made and paws were fixed for histological evaluation. The compound did not show any signs of toxicity and no lethalties were observed.
- 15 Trained lab personnel evaluated the severity and incidence of the arthritic symptoms at regular intervals without knowing which animals had received vehicle or drug.

In Table 9, the mean arthritic score is shown. For each paw, a score ranging from 0 (normal) to 2 (maximal redness and swelling) is given. The score for the 4 paws is summed up and averaged for the 10 animals per group (= Mean arthritic score). Compound 75 clearly suppresses the arthritic score.

Table 9 : Mean Arthritic Score

| Days after immunization | Vehicle (2x) | Compound 75-100 mpk (2x) |
|-------------------------|--------------|--------------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.28 | 0.05 |
| 27 | 1.53 | 0.60 |
| 29 | 4.23 | 0.90 |

-28-

| Days after immunization | Vehicle (2x) | Compound 75-100 mpk (2x) |
|-------------------------|--------------|--------------------------|
| 31 | 4.65 | 1.03 |
| 34 | 5.08 | 0.80 |
| 36 | 4.95 | 0.75 |
| 37 | 4.90 | 0.80 |

Table 10 shows the incidence of arthritis. In the vehicle group the incidence is 9 or 10 animals per group. The incidence for the group treated with Compound 75 is 7 or 8 animals out of 10.

5

Table 10 : Incidence of arthritis (% of animals affected)

| Days after immunization | Vehicle (2x) | Compound 75-100 mpk (2x) |
|-------------------------|--------------|--------------------------|
| 22 | 0 | 0 |
| 24 | 30 | 20 |
| 27 | 60 | 40 |
| 29 | 90 | 80 |
| 31 | 90 | 70 |
| 34 | 100 | 60 |
| 36 | 100 | 70 |
| 37 | 100 | 60 |

Table 11 summarizes the results of the observations for the occurrence of ankylosis as the arthritis progresses. Each paw is scored as follows : 0 for no ankylosis, 1 for ankylosis. Again the results for the four paws are summed up and averaged for the 10 animals. At the end of the experiment, the ankylosis score in the vehicle group (3.1) is clearly higher than that in the group treated with Compound 75 (1.2).

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Table 11 : Ankylosis score

| Days after immunization | Vehicle (2x) | Compound 75 100 mpk (2x) |
|-------------------------|--------------|--------------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.00 | 0.00 |
| 27 | 0.70 | 0.30 |
| 29 | 2.20 | 0.80 |
| 31 | 2.30 | 1.10 |
| 34 | 2.90 | 1.20 |
| 36 | 3.70 | 1.40 |
| 37 | 3.10 | 1.20 |

In Table 12, the incidence of ankylosis is given. In the vehicle group the incidence is 90 to 100 %, but only 60 % in the group of animals treated with Compound 75.

5 Table 12 : Incidence of ankylosis (% of animals affected)

| Days after immunization | Vehicle (2x) | Compound 75 -100 mpk (2x) |
|-------------------------|--------------|---------------------------|
| 22 | 0 | 0 |
| 24 | 0 | 0 |
| 27 | 50 | 10 |
| 29 | 80 | 50 |
| 31 | 90 | 50 |
| 34 | 100 | 50 |
| 36 | 100 | 60 |
| 37 | 100 | 60 |

In Table 13 the mean number of affected paws in the vehicle and compound treated test animals is shown ; compound 75 reduces that number.

10 Table 13 : Mean number of affected paws

| Days after immunization | Vehicle (2x) | Compound 75 -100 mpk (2x) |
|-------------------------|--------------|---------------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.40 | 0.20 |
| 27 | 1.60 | 0.80 |
| 29 | 2.80 | 1.30 |
| 31 | 2.80 | 1.70 |
| 34 | 3.30 | 1.20 |
| 36 | 3.20 | 1.30 |
| 37 | 3.20 | 1.30 |

In conclusion, oral administration twice daily of compound 75 to test animals wherein arthritis is induced by collagen type II, reduces the mean arthritic score ; the beneficial effect is due to both a reduction of the severity (lower score per paw) and a reduction of the incidence (fewer paws affected).

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Example 2 : Therapeutic treatment

Male DBA1/J mice were immunized intradermally with collagen type II emulsified in complete Freund's Adjuvant on day 0 and day 21. Treatment of mice was started on day 30 (10 animals/treatment group ; the animals were randomized so that both groups had similar arthritic symptoms at the start). Mice were treated orally with vehicle [DMSO : cremophor : 0.9 % NaCl solution, 1:1:8 (v:v:v)] or compound 75 at a dose of 100 mg/kg. Three times per week symptoms of arthritis were scored. Animals were treated till day 49, at day 50 animals were sacrificed, blood was collected for analysis of anti-collagen antibodies, and radiographs were. The compound did not show any signs of toxicity and no lethalties were observed.

Trained lab personnel evaluated the severity and incidence of the arthritic symptoms at regular intervals without knowing which animals had received vehicle or drug.

In Table 14, the mean arthritic score is shown. For each paw, a score ranging from 0 (normal) to 2 (maximal redness and swelling) is given. The score for the 4 paws is summed up and averaged for the 10 animals per group (= Mean arthritic score). Compound 75 clearly suppresses the arthritic score.

Table 14 : Mean Arthritic Score

| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.00 | 0.03 |
| 28 | 3.75 | 3.50 |
| 29 | 4.08 | 4.25 |
| 31 | 4.98 | 4.03 |
| 34 | 5.18 | 3.80 |
| 36 | 4.80 | 3.00 |
| 38 | 4.73 | 3.20 |
| 41 | 4.88 | 3.45 |
| 43 | 4.18 | 2.15 |
| 45 | 3.28 | 1.33 |
| 48 | 2.55 | 1.58 |
| 50 | 2.33 | 0.88 |

Table 15 shows the incidence of arthritic symptoms. The incidence is 100 % at the start of treatment. At the end of the treatment period, the incidence in the vehicle

group is reduced to 80%, while in the group treated with compound 75 the incidence is 60%.

Table 15 : Incidence of arthritis (% of animals affected)

| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 22 | 0 | 0 |
| 24 | 0 | 10 |
| 28 | 90 | 90 |
| 29 | 100 | 100 |
| 31 | 100 | 100 |
| 34 | 100 | 100 |
| 36 | 100 | 90 |
| 38 | 100 | 90 |
| 41 | 100 | 90 |
| 43 | 100 | 90 |
| 45 | 80 | 100 |
| 48 | 90 | 60 |
| 50 | 80 | 60 |

5.

Table 16 summarizes the results of the observations for the occurrence of ankylosis as the arthritis progresses. Each paw is scored as follows : 0 for no ankylosis, 1 for ankylosis. Again the results for the four paws are summed up and averaged for the 10 animals. Ankylosis starts to occur around day 30. During the whole treatment period, ankylosis is lower in the drug treated group than in the vehicle treated group.

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Table 16 : Ankylosis score

| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.00 | 0.00 |
| 28 | 0.00 | 0.00 |
| 29 | 0.00 | 0.00 |
| 31 | 1.40 | 0.80 |
| 34 | 3.00 | 2.50 |
| 36 | 3.10 | 2.40 |
| 38 | 3.00 | 2.60 |
| 41 | 2.60 | 1.70 |
| 43 | 3.00 | 2.20 |
| 45 | 2.60 | 1.90 |

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| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 48 | 2.90 | 2.10 |
| 50 | 1.20 | 0.80 |

In Table 17, the incidence of ankylosis is given. No clear difference between the vehicle and drug treated groups can be observed.

5 Table 17 : Incidence of ankylosis (% of animals affected)

| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 22 | 0 | 0 |
| 24 | 0 | 0 |
| 28 | 0 | 0 |
| 29 | 0 | 0 |
| 31 | 90 | 60 |
| 34 | 100 | 90 |
| 36 | 100 | 90 |
| 38 | 100 | 100 |
| 41 | 80 | 70 |
| 43 | 100 | 80 |
| 45 | 80 | 80 |
| 48 | 90 | 90 |
| 50 | 40 | 40 |

In Table 18 the mean number of affected paws in the vehicle and compound treated test animals is shown ; compound 75 reduces that number.

10 Table 18 : Mean number of affected paws

| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 22 | 0.00 | 0.00 |
| 24 | 0.00 | 0.10 |
| 28 | 2.20 | 2.40 |
| 29 | 2.50 | 2.70 |
| 31 | 2.90 | 2.80 |
| 34 | 3.00 | 2.60 |
| 36 | 3.00 | 2.20 |
| 38 | 2.90 | 2.60 |
| 41 | 3.00 | 2.40 |

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| Days after immunization | Vehicle | Compound 75-100 mpk |
|-------------------------|---------|---------------------|
| 43 | 2.70 | 2.20 |
| 45 | 2.50 | 1.90 |
| 48 | 2.50 | 1.50 |
| 50 | 1.90 | 1.20 |

In table 19, the radiographic score of the individual mice is depicted. For each paw, a score ranging from 0 (normal) to 2 (deformation of the whole paw was given. The scores of the four paws are summed up.

5

Table 19 : Radiographic score of individual mice

| | Vehicle | Compound 75-100 mpk |
|-----------|---------|---------------------|
| | 0.5 | 3.0 |
| | 1.5 | 4.75 |
| | 1.25 | 2.0 |
| | 5.00 | 2.5 |
| | 5.25 | 2.5 |
| | 2.5 | 1.0 |
| | 4.0 | 0.0 |
| | 7.0 | 0.0 |
| | 6.5 | 5.25 |
| | 6.5 | 2.0 |
| Average : | 4.0 | 2.3 |
| Median : | 4.5 | 2.25 |

In conclusion, oral administration of compound 75 to mice with established reduces the arthritic symptoms (paw swelling, occurrence of ankylosis and deterioration of the joints as observed on radiographs).

10

Example 3 : *Mycobacterium butyricum*-induced arthritis in Lewis rats

Male SPF-bred Lewis rats (Charles River; 225-275 g) were housed in individual cages under standard laboratory conditions ($21 \pm 2^\circ \text{C}$; $65 \pm 15\%$ relative humidity; light-dark cycle set at 12 h). *Mycobacterium butyricum* (heat-killed and suspended in paraffin oil at 5 mg/ml; 0.05 ml) was inoculated intradermally at the tail base of the rats. On day 14 after inoculation, the diameters (\varnothing) of the hind paws and tibiotarsal joints ($\Sigma \varnothing 14$) were compared with the initial diameters ($\Sigma \varnothing 0$) and rats with a

15

significant swelling ($\Delta\varnothing_{14-0} \geq 6.0$ mm) were assigned to the various treatment groups ($n = 6$; one with a moderate, one with an intermediate, and one with a high increase).

Body weight and paw diameters were measured at days 14 and after 1-week treatment at day 21. Diet consumption was also measured and the number of dead animals on day 21 was noted. Paw swelling at day 21 was expressed as a percentage of the initial inflammation at the start of the treatment (day 14). Control animals were included in each experimental session. Test compounds were administered via a medicated diet. For that purpose, compounds were mixed with ground pellets in proportion to give an approximate daily dose. This medicated diet was administered ad libitum during the experimental period. The real dose was calculated by multiplying the consumed amount of diet with the concentration of the test compound in the diet.

Based on a frequency distribution of a series of control data ($n = 181$), all-or-nothing criteria for drug-induced effects were established. The averaged body weight change during the 1 week experimental period in the control population was a decrease of 7 g. Only 8 out of the 186 control rats (4.3%) showed a decrease of body weight of more than 21 g, which was adopted as criterion for worsening of the *Mycobacterium*-induced decrease of body weight gain. Only 5 out of the 186 control rats (2.7%) showed an increase of body weight of more than 10 g, which was adopted as criterion for reversal of the *Mycobacterium*-induced decrease of body weight gain. In the same set of control animals, paw swelling at day 21 was on the average 117% of the initial value at day 14. Only 4 rats (2.1%) showed a percent swelling below 80%, which was adopted as criterion for anti-inflammatory activity. Sixteen control rats (8.6%) showed a percent swelling above 150%, which was adopted as a criterion for a tendency towards pro-inflammatory activity. Five control rats (2.7%) showed a percent swelling above 170%, which was adopted as a criterion for pro-inflammatory activity.

In table 20, the results obtained with different doses of compound 75 are summarized

| Dose (mg/kg) | # | % change in body-weight | | | % change in swelling | | | |
|-----------------|---|----------------------------|---------|------|----------------------|----------|----------|------|
| | | # < -21% | # > 10% | Mean | # < 80% | # > 150% | # > 170% | Mean |
| 160 | 6 | 4 | 0 | -24% | 3 | 0 | 0 | 79% |
| 80 | 6 | 4 | 0 | -19% | 3 | 0 | 0 | 86% |
| 40 | 6 | 0 | 0 | -9% | 0 | 0 | 0 | 94% |

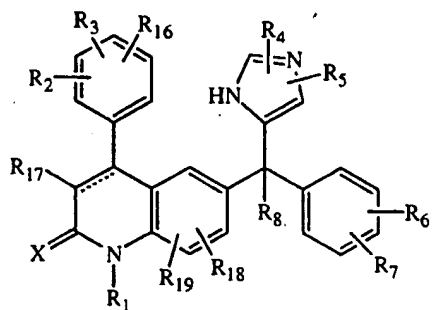
: number of animals

Claims

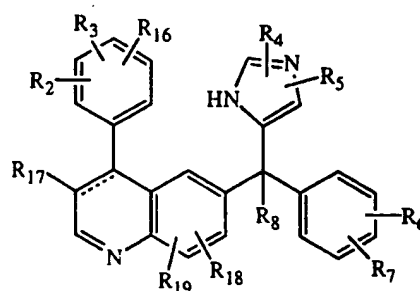
1. Use of at least a farnesyl protein transferase inhibitor for the preparation of a pharmaceutical composition for treating arthropathies.

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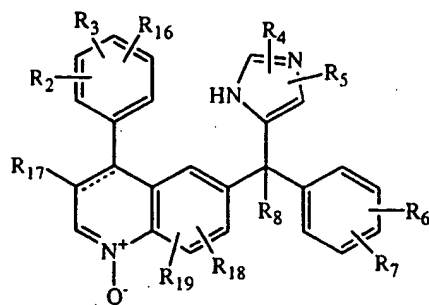
2. The use of claim 1 wherein said farnesyl protein transferase inhibitor is a compound of formula (I), or a compound of formula (II) or (III) which is metabolized *in vivo* to a compound of formula (I), said compounds being represent by



(I)



(II)



(III)

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a stereoisomeric form thereof, a pharmaceutically acceptable acid or base addition salt thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

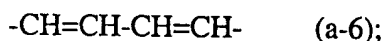
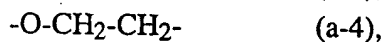
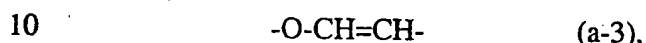
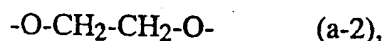
15

R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridyl-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, aminoC₁₋₆alkyl, or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

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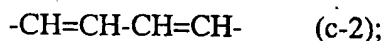
R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

5 R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino- C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2oxy , Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_2 -6alkenyl, 4,4-dimethyloxazolyl; or when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula



15 R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

20 R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, Ar^2oxy , trihalomethyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, or when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula



25 R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylcarbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, carboxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, imidazolyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy- C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, or a radical of formula



wherein R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^1 , Ar^2C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, a radical or formula $-Alk^2-OR^{13}$ or $-Alk^2-NR^{14}R^{15}$;

35 R^{11} is hydrogen, C_{1-12} alkyl, Ar^1 or Ar^2C_{1-6} alkyl;

R^{12} is hydrogen, C_{1-6} alkyl, C_{1-16} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylaminocarbonyl, Ar^1 , Ar^2C_{1-6} alkyl,

- C₁₋₆alkylcarbonylC₁₋₆alkyl, a natural amino acid, Ar¹carbonyl,
 Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxy-
 C₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl,
 di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino,
 5 C₁₋₆alkylcarbonylamino,
 or a radical of formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵,
 wherein Alk² is C₁₋₆alkanediyl;
 R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl,
 hydroxyC₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;
 10 R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;
 R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or
 Ar²C₁₋₆alkyl;
 R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;
 R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;
 15 R¹⁹ is hydrogen or C₁₋₆alkyl;
 Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy
 or halo; and
 Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy
 or halo.
- 20 3. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein X is oxygen.
- 25 4. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein the dotted line represents a bond.
- 30 5. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein R¹ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy-
 C₁₋₆alkyl or mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl.
6. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein R³ is hydrogen and R² is halo, C₁₋₆alkyl,
 C₂₋₆alkenyl, C₁₋₆alkyloxy, trihalomethoxy or hydroxyC₁₋₆alkyloxy.
- 35 7. The use of claim 2 wherein said farnesyl protein transferase inhibitor is a
 compound of formula (I) and wherein R⁸ is hydrogen, hydroxy, haloC₁₋₆alkyl,
 hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, imidazolyl, or
 a radical of formula -NR¹¹R¹² wherein R¹¹ is hydrogen or C₁₋₁₂alkyl and R¹² is

hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, or a radical of formula -Alk²-OR¹³ wherein R¹³ is hydrogen or C₁₋₆alkyl.

8. The use of claim 2 wherein the compound is
 - 5 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)-methyl]-1-methyl-2(1*H*)-quinolinone,
6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-
10 phenyl)-1-methyl-2(1*H*)-quinolinone;
6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride monohydrate;
6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxy-
15 phenyl)-1-methyl-2(1*H*)-quinolinone, and
6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salts thereof.
9. The use of claim 2 wherein the compound is
 - 20 (+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone; or a pharmaceutically acceptable acid addition salt thereof.
10. The use of any one of the preceding claims wherein a therapeutically effective
 - 25 amount of the pharmaceutical composition is administered orally or parenterally.
11. The use of claim 9 wherein the pharmaceutical composition is administered orally
 - 30 in an amount of from 100 to 1,500 mg daily, either as a single dose or subdivided into more than one dose.
12. The use of claim 1 wherein the arthropathy is rheumatoid arthritis, osteoarthritis,
 - 35 juvenile arthritis, polyarthritis, gout, epidemic polyarthritis (Ross River Virus infection), psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus ; or the arthropathy observed in Felty's syndrome, Reiter's syndrome or Still's syndrome.

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13. A method of treating arthropathies in a mammal comprising the steps of administering a therapeutically effective amount of a farnesyl protein transferase inhibitor to said mammal.

INTERNATIONAL SEARCH REPORT

Application No
PCT/EP 99/04546

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 5 574 025 A (ANTHONY NEVILLE J ET AL) 12 November 1996 (1996-11-12) abstract column 11, line 56 -column 12, line 7 --- | 1, 10, 12, 13 |
| P, X | WO 98 43629 A (JUNIEU JEAN LOUIS ; SEMPLÉ GRAEME (GB); KENDRICK DAVID ALAN (NL); F) 8 October 1998 (1998-10-08) abstract page 6, paragraphs 1, 2 page 8, paragraph 8; claim 3 --- | 1, 10, 12, 13 |
| A | WO 97 21701 A (JANSSEN PHARMACEUTICA NV ; VENET MARC GASTON (FR); ANGIBAUD PATRICK) 19 June 1997 (1997-06-19) the whole document --- -/-- | 2-9 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

21 October 1999

Date of mailing of the international search report

29/10/1999

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Authorized officer

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INTERNATIONAL SEARCH REPORT

National Application No

PLT/EP 99/04546

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P,A | WO 98 40383 A (JANSSEN PHARMACEUTICA NV ;ANGIBAUD PATRICK RENE (FR); LIGNY YANNIC) 17 September 1998 (1998-09-17) the whole document --- | 2-9 |
| P,A | WO 98 55124 A (JANSSEN PHARMACEUTICA NV ;END DAVID WILLIAM (US); ZELESKO MICHAEL) 10 December 1998 (1998-12-10) the whole document ----- | 2-9 |

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/04546

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,10,12,13 relate to a use/method defined (inter alia) by reference to the following parameter:
P1:farnesyl protein transferase inhibitor

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the use of compounds of formula I-III of claims 2-9,11 and the general idea underlying the present application.

A compound or group of compounds is not sufficiently defined only by its pharmacological parameters or properties: for a fully valid definition of a compound or a group of compounds, a structural definition is needed. A complete search is virtually impossible because it is not exhaustively known which chemical compounds are comprised by the scope of the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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